list

ATTACHMENT L

An Empirical Evaluation of the Application of the Dioxin Toxicity Equivalency (TEQ) Method to PCB Mixtures

Introduction

The U.S. Environmental Protection Agency (EPA) has evaluated the potential cancer risks of polychlorinated biphenyls (PCBs) using conservative animal models and PCB-specific data for over 20 years. In 1996, EPA thoroughly reviewed both the animal and human data, and developed a range of cancer slope factors (CSFs) for use in PCB risk assessments (EPA, 1996). The upper bound of this range was set at 2 $(mg/kg\text{-}day)^{-1}$, a value lower than that previously used by the Agency. In its 1996 reassessment, EPA's approach characterized the potency of the entire PCB mixtures (i.e., Aroclors). According to EPA, "[t]hese mixtures contain overlapping groups of congeners that, together, span the range of congeners most often found in environmental mixtures" (EPA, 2003). Such PCB mixtures include both so-called *dioxin-like* and *non-dioxin-like* compounds.

In its Human Health Risk Assessment (HHRA) of the Housatonic River, EPA has evaluated the potential cancer risks of total PCBs using the upper-bound CSF for PCBs that was recommended in the Agency's 1996 reassessment and is set forth on IRIS (EPA, 2003). In addition, the HHRA uses the toxicity equivalency (TEQ) method to calculate potential cancer risks associated with dioxins, furans, and the dioxin-like PCB congeners – all converted to toxicity equivalents of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) – and it adds those risks to the risks calculated for total PCBs.

Originally, the TEQ approach was developed for screening risks from dioxins and furans in combustion sources and incinerator emissions (Eadon et al., 1986). Under that approach, the concentrations of the various dioxin and furan compounds are converted to TEQs of TCDD (believed to be the most potent dioxin compound) through the use toxicity equivalency factors (TEFs), which are based on the assumed toxicity of such compounds relative to that of TCDD; and the resulting total TEQ concentration is then evaluated for potential cancer risks through the use of a CSF for TCDD. The application of this approach to PCB congeners is more recent and more controversial. Although the use of that approach for PCBs was briefly mentioned in EPA's 1996 reassessment of PCB cancer risks (EPA, 1996), that approach is described in detail and utilized in EPA's draft Dioxin Reassessment (EPA, 2000), which has not been finalized by EPA and remains under scientific review. In fact, as discussed in the text of these comments, Congress has called for that document, including the application of the TEQ approach to PCBs, to be reviewed by the National Academy of Sciences (NAS) (House of Representatives, 2003).

When the TEQ approach is applied to PCBs, the concentrations of the dioxin-like PCB congeners within a PCB mixture are converted to TEQs of TCDD using various TEFs. Twelve of the 209 PCB congeners have been assigned dioxin-like toxicity, primarily based on their structural similarity to dioxins, their ability to induce activity in certain enzymes, and their ability to bind to the aromatic hydrocarbon receptors in animal cells. The TEFs for these 12 PCB congeners are based on a variety of endpoints demonstrated in *in vitro* assays and *in vivo* animal studies, most of which are non-cancer endpoints (Van den Berg et al., 1998). Once the TEQs have been calculated for the various dioxin-like congeners, they are summed to determine a total TEQ concentration, and the CSF for TCDD is then applied to quantify the potential risks associated with estimated exposures to those congeners.

To evaluate the application of the TEQ methodology in estimating the cancer potency of PCB mixtures, we tested the approach empirically using the results from 2-year cancer bioassays involving four PCB mixtures of known composition that were fed to Sprague-Dawley (SD) rats and from a 2-year cancer bioassay of SD rats that had been fed TCDD. Our present study involved two components. First, the effective CSFs in SD rats were determined for the TEQ components of each PCB mixture and compared to that of TCDD. A basic precept of the TEQ method is that a given dose of TEQ has equal biological potency irrespective of the chemical mixture from whence it came. Thus, each CSF determined in this way should be equivalent to that of TCDD, if the tenet is correct.

Second, we determined the human CSFs for three PCB mixtures using the proposed TEQ methodology and compared these CSFs to the empirically developed CSFs cited by EPA (1996; 2003) for the respective mixtures, which included both dioxin-like and non-dioxin-like PCB congeners. If the TEQ method were an accurate predictor of the potency of the dioxin-like PCBs in a PCB mixture, then one would expect the CSFs determined via the TEQ method to be consistent with the CSFs derived empirically for the PCB mixtures.

Materials and Methods

Data Source. A comprehensive chronic toxicity and oncogenicity feeding study of four PCB mixtures was performed (Brunner et al., 1996), and the findings associated with the carcinogenicity segment of the study have been published (Mayes et al., 1998). This study was conducted on male and female Sprague-Dawley (SD) rats using four PCB mixtures with varying degrees of chlorination (Aroclors 1016, 1242, 1254, and 1260). In each group, the animals received feed containing PCBs for 7 days/week for 24 months. Two or three dose rates plus controls were employed for each PCB mixture tested. EPA has stated that this study "provides the most comprehensive information for empirical modeling" (EPA, 1996, p. 34).

For each PCB mixture, the concentrations of the dioxin-like PCB congeners within the mixture were converted to TCDD TEQs using the TEF scheme developed by the World Health Organization (Van den Berg et al., 1998) and used in the HHRA. Once the TEQs were calculated for the various dioxin-like congeners, they were summed to determine a total TEQ concentration for each PCB mixture. These TEQ concentrations were then used in the dose-response assessment using the EPA benchmark dose model along with the survival-adjusted Brunner et al. (1996) animal bioassay data (Mayes et al., 1998) in two separate sets of calculations described below. Only data for the female rats were included since the male rats showed no statistical elevation in tumor incidence except for those exposed to Aroclor 1260, but even in this instance only at the 100-ppm dose level. For 2,3,7,8-TCDD, the two-year rodent bioassay of Kociba et al. (1978), with the Pathology Working Group (PWG, 1990a, 1990b) reevaluation of liver pathology and corresponding tumor incidence data, was used in the dose-response assessment. Because 2,3,7,8-TCDD has a TEF of 1, the doses of TCDD were modeled directly as TEQ in the dose-response model.

Determination of Effective CSFs for TEQ Components of PCB Mixtures and of 2,3,7,8-TCDD. In this analysis, a rodent CSF was determined for the TEQ in each PCB mixture that had been administered to SD rats using the EPA benchmark dose software. We also developed a rodent CSF for TCDD using the EPA benchmark dose software (EPA, 2001). In each CSF determination, whether for the TEQ concentrations in each PCB mixture or for TCDD itself, we derived CSFs only for the SD rats in order to facilitate comparisons on an equivalent basis. In each instance, the values represent rodent CSFs, because an inter-species extrapolation to humans involving either body weight or half-life scaling assumptions was not made. Thus, a simple direct comparison of the TEQ CSFs and the CSF for TCDD was possible. If the dioxin toxic equivalency method is predictive of the potency of dioxin-like PCB congeners, then the CSFs for TEQs in each PCB mixture should be equivalent, or nearly so, to each other and to the rodent CSF for TCDD.

Comparison of Human CSFs for PCB Mixtures Using TEQ Methodology with Empirically Derived CSFs for Those Mixtures. In this analysis, human CSFs were determined using the TEQ methodology for each of the Aroclor mixtures and were compared to the results of CSFs calculated empirically for those mixtures using standard EPA methodologies. The TEQ-based CSFs for the mixtures were obtained by multiplying the concentration of the TEQ in each mixture by a CSF for TCDD. The steps involved in making these calculations are detailed below. In contrast to the previous set of comparisons, this analysis inherently included inter-species extrapolations from rats to humans involving the use of either body weight or half-life scaling assumptions that are implicit in the selection of the TCDD CSF used in the analysis.

To make this comparison, it was first necessary to calculate TEQ-based CSFs for several PCB mixtures (Aroclors 1242, 1254, and 1260). This was done by following a sequence of four steps.

- Step 1 – identify the fraction of each "dioxin-like" congener in each PCB mixture. The fractions of "dioxin-like" congeners in PCB mixtures have been determined with a variety of high-resolution gas chromatographic analytical methods, and are reported in Frame et al. (1996), Frame (1997), and Schultz et al. (1989).[1]

- Step 2 – multiply the fraction of each "dioxin-like" congener in the PCB mixture by its respective TEF (Van den Berg et al., 1998) to calculate the fractional TEQ of the PCB mixture attributable to each congener.

- Step 3 – sum the fractional TEQs across "dioxin-like" congeners to yield the total TEQ of the PCB mixture relative to pure TCDD.

[1] For purposes of this analysis, the fractions of dioxin-like congeners in PCB mixtures were computed as the mean of the data from Frame et al. (1996) and Frame (1997). (It should be noted that the data from Schultz et al. (1989) would not significantly alter the results presented herein.) Because the fractions of dioxin-like congeners in Aroclor 1016 were below the limit of detection in these papers, this analysis could not be completed for that mixture.

♦ Step 4 – multiply the total TEQ of the PCB mixture by a CSF for TCDD to derive the TEQ-based CSF for the mixture. For purposes of this analysis, we have used both the TCDD CSF of 150,000 $(mg/kg\text{-}day)^{-1}$, which was used in the main HHRA, and the draft TCDD CSF of 1,000,000 $(mg/kg\text{-}day)^{-1}$, which was proposed in EPA's draft Dioxin Reassessment document (EPA, 2000) and is discussed in the uncertainty analyses of the HHRA. (As discussed in Attachment M to the present set of Comments, GE does not accept the validity of either of these CSFs; they are used here for illustrative purposes.)[2]

Results

Results of the benchmark dose modeling to derive the rodent CSFs for the TEQs present in the four PCB mixtures as well as for TCDD are presented graphically in Figure 1 (next page). Comparison of the rodent CSFs generated for the TEQ present in each PCB mixture shows disparities that are significant and are not uniform across Aroclors [CSFs of 220,000; 16,000; 8,900; and 50,000 $(mg/kg\text{-}d)^{-1}$]. The modeled CSFs for the TEQ in PCB mixtures vary by approximately 24-fold across the mixtures tested. Moreover, these modeled CSFs do not match the 2,3,7,8-TCDD CSF of 9,600 $(mg/kg\text{-}day)^{-1}$ that was determined empirically from Kociba's animal bioassay of TCDD.[3] These comparisons clearly demonstrate that the TEQ component in each of the PCB mixtures, as determined through the use of the TEFs in Van den Berg et al. (1998), does not have the same potency as TCDD.

In the second component of our evaluation, the calculated human CSFs using the TEQ methodology for three PCB mixtures involved are shown below, together with the empirically derived CSFs cited by EPA (1996; 2003) for those PCB mixtures[4]:

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[2] Note that use of this four-step procedure produces CSFs only for the dioxin-like congeners in the mixtures. Under the approach used in the HHRA, total PCBs are evaluated using a CSF developed for PCBs, and the two sets of risks are added to produce an overall carcinogenic risk – a procedure which, as noted below, results in double counting the potency of the dioxin-like congeners.

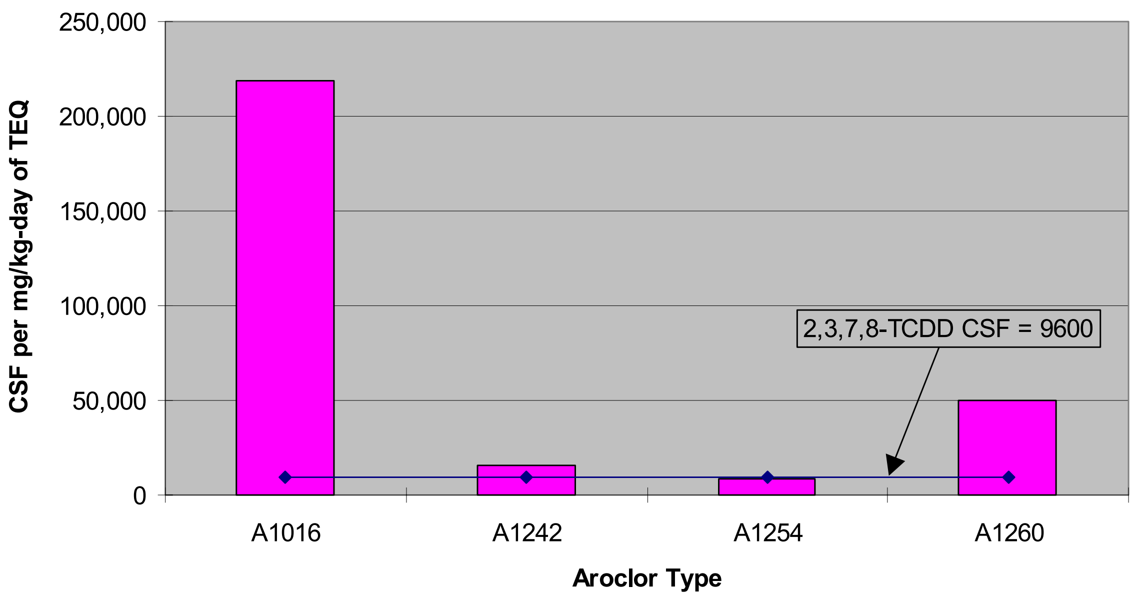
[3] The rodent CSF for 2,3,7,8-TCDD of 9,600 $(mg/kg\text{-}day)^{-1}$ is different from the CSF of 30,000 $(mg/kg\text{-}day)^{-1}$ that we have recommended for humans in Appendix M because no inter-species scaling from rodents to humans is reflected in the CSF of 9,600 $(mg/kg\text{-}day)^{-1}$.

[4] These Aroclor-based CSFs are the upper-bound CSFs reported by EPA (1996) that were derived based on the results from the comprehensive chronic toxicity and oncogenicity feeding study performed by Brunner et al. (1996) and published by Mayes et al. (1998).

Aroclor	TEQ-Based CSF (with TCDD CSF of 150,000)	TEQ-Based CSF (with TCDD CSF of 1,000,000)	Aroclor-Based CSF
Aroclor 1242	0.73 $(mg/kg\text{-}day)^{-1}$	4.7 $(mg/kg\text{-}day)^{-1}$	0.4 $(mg/kg\text{-}day)^{-1}$
Aroclor 1254	6.6 $(mg/kg\text{-}day)^{-1}$	43 $(mg/kg\text{-}day)^{-1}$	1.5 $(mg/kg\text{-}day)^{-1}$
Aroclor 1260	1.0 $(mg/kg\text{-}day)^{-1}$	6.5 $(mg/kg\text{-}day)^{-1}$	0.5 $(mg/kg\text{-}day)^{-1}$

The calculated TEQ-based CSFs are greater than the mixture-derived CSFs by varying amounts. As these comparisons illustrate, use of the TEQ approach to calculate carcinogenic risks of PCBs substantially overpredicts the carcinogenic potency of PCBs relative to the actual potencies demonstrated in laboratory bioassays.

Figure 1. Calculated Rodent CSFs for TEQ in PCB Mixtures and for 2,3,7,8-TCDD



Discussion

The dioxin toxic equivalency hypothesis requires that any unit of TEQ is equivalent to any other unit in terms of biological potency, regardless of its origin (i.e., from dioxin-like congeners or TCDD itself) and regardless of the medium in which it exists. This is a difficult requirement to meet, since it necessitates that effects such as antagonism resulting from competition for receptor sites by other molecules in the mixtures, species differences, and differences in dose-response curves be insignificant. All of these issues have been tested experimentally and conformance of experimental results with the hypothesis has been inconsistent. Also implicit in this hypothesis is that relative potencies, largely based on initial cellular responses to these chemicals, such as enzyme induction, apply equally well to complex disease outcomes, such as tumorigenesis.

The current study reveals that the modeled rodent CSFs for the TEQ in PCB mixtures varied by approximately 24 fold. In addition, these modeled CSFs did not match the CSF that has been determined empirically for TCDD.[5] In addition, this study demonstrates that the use of the TEQ method resulted in TEQ-based CSFs for PCB mixtures that were considerably higher than the CSFs that have been determined empirically from the rodent bioassays using conventional EPA methodologies. In both cases, the findings are in sharp contrast to the results that one would expect if the fundamental premise of the TEQ method were true. Thus, both analyses indicate that there is a fundamental shortcoming associated with the use of the TEQ approach for estimating the carcinogenic potential of PCB mixtures. Some potential explanations for this are discussed below.

Initially, the TEQ approach was developed to provide a method for including compounds without toxicity data in a risk calculation. Expanding the scheme to include PCBs was based on the finding that the 12 coplanar PCB congeners exhibited some structural and biochemical similarities to 2,3,7,8-TCDD. Safe (1990) hypothesized that responses to such compounds are mediated through binding with a common receptor protein, the aryl hydrocarbon receptor (AhR), and involve the induction of various cytochrome P-450 enzymes, including aryl hydrocarbon hydroxylase (AHH) and 7-ethoxyresorufin-o-deethylase (EROD). Using the TEFs to predict carcinogenicity assumes that <u>if</u> a compound has the ability to induce these enzymes, it also has the ability to result in a carcinogenic response. This assumption, in fact, may not be true. For most of the 12 PCB congeners, there are limited or no carcinogenicity data available. The majority of the TEFs are based on enzyme induction studies and body and organ weight effects (Van den Berg et al., 1998). As examples, the TEF assigned for PCB congener 169 is based on

[5] Although this study based the comparisons on the use of rodent CSFs, the same points would hold true if equivalent inter-species scaling factors had been applied to each CSF to convert them to human CSFs. Thus, these observations and conclusions would not change regardless of the specific CSF selected for 2,3,7,8-TCDD.

EROD induction and thymic atrophy, and the TEF assigned for PCB congener 77 is based on EROD induction and hepatic retinol decreases. Thus, an extrapolation from endpoints such as body/organ weight changes and enzyme induction to tumorigenesis may not be as well correlated as previously thought.

In addition, since TEQs equate the toxicity of PCB congeners to that of TCDD (at any dose or concentration), the approach necessarily assumes that the dose-response curves for those congeners are parallel to that for TCDD. In order for TEFs to remain constant over the range of the doses or concentrations in the dose-response curve, both the shape of the dose-response curve and the maximum response must be the same for the PCB congeners and for 2,3,7,8-TCDD. However, non-parallel dose-response curves for 2,3,7,8-TCDD and dioxin-like PCB congeners have been reported. Safe (1990), for example, evaluated the relative dose response for various dioxin, furan, and PCB congeners in terms of the potencies associated with different endpoints and different species and showed that the relative potencies varied by more than an order of magnitude depending on the endpoints considered. When comparing the relative potency of TCDD to that of 3,3',4,4',5-pentachlorobiphenyl at the EC_{50} levels in rats, Safe reported that TCDD was 66 times more potent for body weight loss, 8 times more potent for thymic atrophy, and 125 times more potent for AHH induction. It appears that, at least for certain PCB congeners, the dose-response curves are not parallel to that for TCDD. Most recently, Toyoshiba et al. (2002), in a NIEHS study, demonstrated that the dose-response pattern for PCB 126 was not consistent with the pattern expected under the TEF assumption.

The TEQ approach further assumes that the toxicities of all individual PCB congeners in a mixture are additive. Knowledge of the mechanisms by which AhR-active chemicals cause effects suggests that the PCB congeners' toxicities represented by TEFs should not be additive. An understanding of the AhR mechanism substantially weakens the primary assumption of the TEQ approach that the potencies of individual agonists can be summed to predict the potency of a mixture of agonists in the body. Where antagonists are present in concentrations higher than the concentration of agonists, it is difficult for agonists to bind to receptors. Moreover, partial agonists or incomplete agonists compete with complete agonists for receptor binding sites. Thus, whenever a human body contains a mixture of complete agonists, partial agonists, and antagonists, the total impact on the body cannot be predicted by the sum of the various agonist concentrations (Goldstein et al., 1990).

Empirical data indicate that PCB Aroclor mixtures may have some antagonistic properties. For example, Safe (1990) reported that Aroclor 1254 acts as a competitive antagonist to TCDD. Harper et al. (1995) investigated the immunotoxicity of several PCB mixtures and congeners. ED_{50} values for immunosuppressive activity were determined for Aroclors 1260, 1254, 1248 and 1242. TEQs and corresponding ED_{50} values were calculated for these mixtures based on the observed ED_{50} value for the immunosuppressive activity of TCDD (Harper et al., 1995). In comparing the observed ED_{50} values to the calculated ED_{50} values, the authors concluded that "for Aroclors 1254, 1248 and 1242, the high ED_{50} (observed)/ED_{50}(calculated) ratios (i.e., 5.9 to 22.0) indicate that the TEQ approach overestimates the toxicity of these mixtures due to non-additive (antagonistic) interactions of the PCBs" (Harper et al., 1995). Furthermore, Starr et al. (1997) reported that "PCBs and some PCDFs antagonize AhR-mediated responses including fetal cleft palate, hydronephrosis, immunotoxicity, embryotoxicity and induction of CYP1A1-dependent activities." With additivity not established across congeners and endpoints in animal studies, it is not warranted to quantify the toxicity of PCB mixtures on a method that relies upon summing the TEQs for the individual congeners.

In addition to the above points, it is important to note that use of the TEQ approach in combination with assessing the cancer risks from total PCBs using a PCB CSF results in double counting the carcinogenic potential of the dioxin-like congeners in the PCB mixtures. Under the TEQ approach, the available or estimated congener-specific data are used to estimate risks for the dioxin-like congeners through converting them to TCDD TEQs and then applying a CSF for TCDD. However, the existing CSFs for PCBs (EPA, 1996) characterize the carcinogenic potential of the entire PCB mixture, which includes both dioxin-like and non-dioxin-like congeners. If one evaluates total PCBs using a PCB CSF and then evaluates the dioxin-like congeners using dioxin TEQs, as the HHRA has done, then the carcinogenic potential of the dioxin-like congeners is counted twice because their carcinogenic potential is already included in the CSF for PCBs. The HHRA recognizes this potential for double counting, and has made an adjustment in the food consumption assessments (Vol. 1, pp. 2-10 – 2-11), but not in the Direct Contact Assessment (Vol. IIIA, p. 3-7), in an effort to avoid such double counting. However, as detailed in Section 6.1.1.4 of these Comments, the adjustment made by EPA in the HHRA to account for this phenomenon does not adequately address this issue.

Conclusion

The tests we conducted resulted in findings that are inconsistent with the results that would be expected if the TEQ method were an accurate predictor of the cancer potency of PCB mixtures. Based both on these empirical findings and the theoretical reasons discussed above, it can be seen that the TEQ approach does not accurately estimate PCB cancer response and thus should not be used for evaluating potential cancer risks associated with PCBs.

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